

Non-pharmacological pain management in the neonatal intensive care unit: Managing neonatal pain without drugs



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ABSTRACT

Premature infants hospitalized after birth are exposed to repeated painful procedures as part of their routine medical care. Early neonatal exposure to unmanaged pain has been linked to numerous negative long-term outcomes, such as the development of pain hypersensitivity, detrimental psychological symptomatology, and altered neurodevelopment. These findings emphasize the crucial role of pain management in neonatal care. The aim of this article is to give an overview of evidence-based non-pharmacological pain management techniques for hospitalized neonates. Research supporting the effectiveness of various proximal, distal, and procedural pain management methods in neonates will be presented. Additionally, understanding the larger biopsychosocial context of the infant that underpins the mechanisms of these pain management methods is essential. Therefore, two important models that inform non-pharmacological approaches to infant pain management (DIAPR-R [The Development of Infant Acute Pain Responding-Revised], Attachment Theory) will be discussed.

For infants born preterm, painful medical procedures are a routine part of their medical care. Research has demonstrated that approximately 7% of newborns are hospitalized after birth [1] and are subsequently exposed to repeated painful procedures. Previous research has found that neonates in NICUs experience an average of 7.5–17.3 daily painful procedures [2]. Approximately 70% of medical procedures carried out on neonates in the NICU are classified as painful [3]. Additionally, both preterm and term newborns requiring more intensive care, such as respiratory support, are exposed to an increased amount of acute procedures [4]. While it was previously believed that newborns did not feel pain [5], research findings have not only refuted this belief [6], but have also revealed that newborns' threshold for pain is likely lower than that of older infants and children [7] due to developing abilities to modulate pain both cognitively and physically. Moreover, preterm neonates' pain thresholds are seen as substantially lower than full-term newborns [7]. Given the ubiquitous nature of painful and invasive medical procedures in the NICU [8,9], the implications of repetitive painful procedures have also been studied in the literature.

Preterm newborns' length of NICU stay and amount of early exposure to painful procedures are predictive of detrimental psychological symptoms, such as somatization and internalizing symptoms, during their preschool and school years [10,11]. Early neonatal exposure to unmanaged pain has also been linked to altered

neurodevelopmental outcomes in school aged children, such as thinner cortical regions, predominantly those associated with the frontal and parietal lobes [12]. In addition to undermanaged acute pain leading to highly distressing procedures for newborns, research has linked early pain exposure with multiple adverse long-term effects, relating to both subsequent pain reactivity and mental health outcomes. For instance, infants demonstrate a subsequent hypersensitivity to pain with early exposure to painful procedures [13,14]. This also leads to higher distress reactivity perceiving subsequent non-noxious procedures, such as diaper changes, as painful [15].

It is unequivocal that neonates are exposed to an abundance of iatrogenically painful procedures during an exquisitely sensitive period of development, which results in long-term implications that scientists and clinicians are only beginning to understand. Pain management is a critical factor to understand in neonatal care. This article will discuss pain management strategies that focus on cognitive, behavioural and contextual approaches. However, while pain management strategies will be presented, understanding the larger biopsychosocial context of the infant that helps to explain the mechanisms of these approaches is of primary importance. Two important models that should inform nonpharmacological approaches to infant pain management (DIAPR-R [The Development of Infant Acute Pain Responding-Revised], Attachment Theory) will be discussed to set a foundation.

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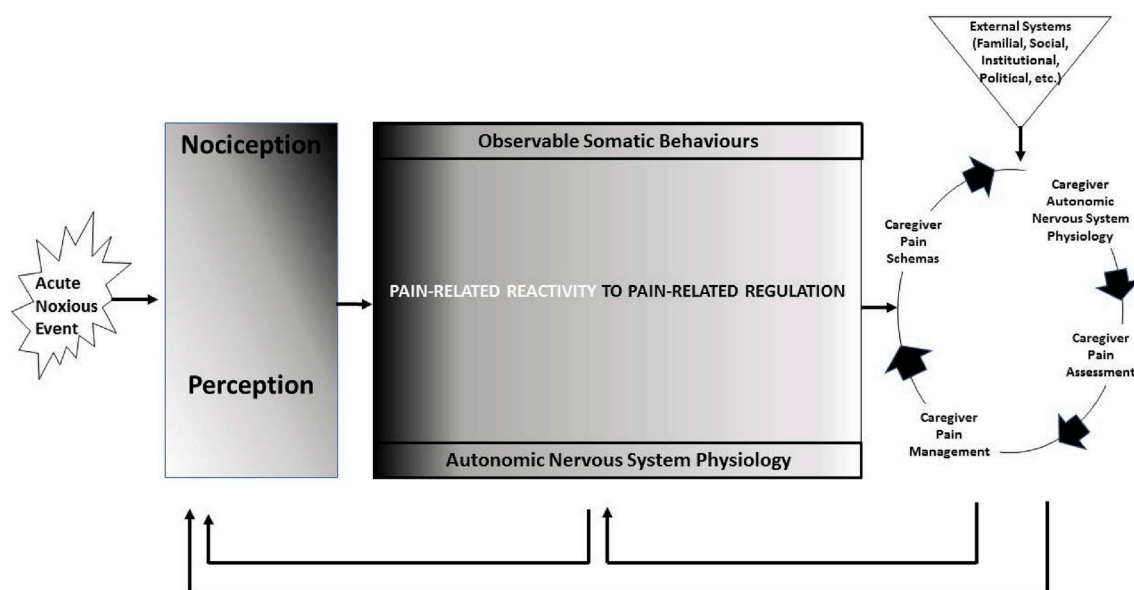


Figure X: The Development of Infant Acute Pain Responding- Revised (DIAPR-R)

Fig. 1. The Development of Infant Acute Pain Responses- Revised (Pillai Riddell 2018, as cited in Goubert, Pillai Riddell, Simons and Borsook, in press).

1. A biopsychosocial model of infant acute pain: the DIAPR-R model

In order to effectively manage infant acute pain, the underlying biological, cognitive, emotional, and social aspects of the pain experience must be understood. Currently, there is only one biopsychosocial model designed to specifically understand infant acute pain from a biopsychosocial perspective - the DIAPR-R [16], See Fig. 1. While based on an extensive program of longitudinal research with the OUCH Cohort (www.yorku.ca/ouchlab) with healthy infants over the first year of life, the relevance to the preterm child is strong. A few key features of the DIAPR-R model deserve highlighting. First, similar to the first version of the model [17], it purports that infants are biologically predisposed to seek the help of others in times of distress. Lacking the physical and cognitive capacity to protect themselves from danger, during periods of distress (such as pain), infant responding must be taken into the context of caregiving. New to the model, based on collaborative work with a neurophysiological research group (Fitzgerald lab, University College London), the model took a stronger attempt to speculate and present the nuances of the biological processing of the event.

Immediately following the painful event, the DIAPR-R model illustrates the progression of the pain response, from the initial **nociception** (marked by the cascade of events from the peripheral nociceptor to the first afferent signals in the primary and secondary somatosensory cortex), to the **perception** of the painful stimulus (characterized by the widespread cortical activation in areas such as the prefrontal cortex, anterior cingulate cortex, insular cortex, and the amygdala), which are associated with the process of making sense of the initial response in the somatosensory cortex [18]. These initial processes combine to inform the infants' **pain-related reactivity** response, which subsequently transitions into a **pain-related regulation** response as the child returns to baseline distress levels. This sequence from nociception and perception to pain-related reactivity followed by pain-related regulation is additionally impacted by the caregiver context, such as the caregivers' cognitions (e.g., pain schemas and assessments), as well as their responses (e.g., caregivers' ANS physiological responses and their engagement in pain management strategies). As aforementioned, the caregiver context is particularly important in neonates, due to their inability to engage in self-directed regulation strategies, thus making it

necessary for them to rely on sources of external distress regulation [19,20]. Moreover, on a broad level, the DIAPR-R model also depicts the infants' larger systemic influences (e.g., culture) as exerting an effect on their pain response via the caregiver [21]. Importantly, the model uses feedback loops to demonstrate the mechanisms via which the caregiver context and the non-immediate pain response feedback on the nociception and perception of pain.

The new DIAPR-R model borrows heavily on a fundamental principle from decades of work in developmental psychology on the Attachment System. Initially formulated by Bowlby [22,23] and operationalized by Ainsworth et al. [24] and Main & Solomon [25], the attachment relationship, i.e. the way in which a child has been socialized by a caregiver throughout early childhood regarding how to involve them to regulate distress, is critical to integrate when understanding psychological (cognitive, behavioural, contextual) perspectives to infant pain management. The next section provides more detail in understanding infant pain within a caregiver context.

2. Infant acute pain and attachment: the importance of the caregiver context

Grounded in Attachment Theory [22,23], the DIAPR-R model emphasizes the caregiver context of infant pain as fundamental to understanding its response. Over the first year of life infants are biologically predisposed to respond in ways that are predicated on having a caregiver present. From an attachment perspective, it is purported that a newborn is born able to signal distress (e.g., crying) in order to achieve physical proximity to their caregiver and alert the caregiver to engage in distress-reducing or mitigating intervention. Alternatively, it is also theorized that parents have an innate system activated by infants' distress signals, which in turn prompts them to respond in a soothing manner that will help regulate the infants' negative affect [26]. Decades of developmental psychology research have demonstrated that repeated caregiver-child interactions in distressing situations subsequently predict children's behaviour in distressing situations, which are operationalized as attachment categorizations (specifically secure, avoidant, resistant, and disorganized). While a detailed primer on Attachment Theory is beyond the scope of the chapter, the following descriptions are offered as a quick heuristic due to its relevance to understanding not only infant pain management but infant pain assessment [27], as so

much of assessing the need and the impact of pain management is based on overt signalling. Secure infants have learned to react vigorously to distress and are more easily regulated post-distress by a caregiver whom they have learned is generally responsive to their distress. Avoidant infants have learned to mute overt distress and attempt to avoid a caregiver because they have learned to be generally rejecting during distress. Resistant infants have learned to amplify and sustain distress signalling to help ensure proximity due to learning their caregiver can be inconsistently responsive. Finally, disorganized infants tend to respond in ways that do not appear to be organized ways of interacting with a caregiver (e.g. a complete lack of behavioural response to distress). Disorganization is often based on having interactions, during distressing situation, with their caregiver where the caregiver is perceived as frightening or otherwise atypical. Disorganization as an outcome should be of particular concern when understanding preterm infants in pain, given the allostatic stress load of repetitive painful procedures in a constrained parental caregiving context. Longitudinal research has suggested NICU infants have a higher chance of attachment disorganization [28]. Moreover, positive caregiver-infant interactions have been demonstrated to exert a buffering effect on the relationships between early neonatal pain exposure in preterm infants and subsequent cognitive functioning and mental health outcomes [29,30].

3. Importance of the caregiver context in neonatal pain management

The above findings point to the importance of caregiver inclusion in the implementation of pain management techniques in hospital settings. This is supported by previous research indicating a positive link between maternal involvement in hospitalized infants' care and newborns' levels of stress and pain [31]. Furthermore, NICU nurses have previously pointed to their heavy workload and the lack of maternal presence in the NICU during infants' medical procedures as some of the main challenges for failing to engage in non-pharmacological pain management strategies, such as skin-to-skin contact [32]. In contrast, 87% of parents of NICU infants have reported a desire to be involved in their children's pain management and, out of those who participated in a study examining attitudes to maternal care in the NICU, 80% indicated it was a positive experience and 90% would wish to be included again [33].

4. Non-pharmacological pain management techniques in neonates

Previous pain management models, such as the "5P" approach [34], which denotes procedural, physical, pharmacological, psychological, and process pain management interventions, have been proven crucial in directing pain management efforts for older infants and children. However, many techniques traditionally used in older infants and children are not appropriate for preterm neonates. For example, distraction has been posited to be more effective in older infants due to the immature motor and cognitive capacities at birth [35]. Moreover, longitudinal work with term infants over vaccinations in the first year of life has suggested that younger infants keep their eyes closed longer, posited to reflect sensory overwhelm and a greater dependence on caregiving [36,37].

Rather than organize in traditional groupings such as the 5P's, owing to the unique context of infancy, the article will proceed based on how the strategies are enacted with neonates, namely proximal, distal, and procedural methods of what is mostly acute pain. However, it is important to note that many of the below strategies reflect attachment principles of proximity to caregiver and increasing feelings of safety/secureness and would be helpful regardless of whether the stressor is painful or not.

A few notes regarding the following review: due to preterm neonates comprising a large proportion of hospitalized newborns in NICUs,

the bulk of the data presented below will originate from research with preterm, as opposed to full term, neonates. Therefore, the nature of the sample (preterm versus full term) will only be specified if a study is based on full term neonates. Moreover, whenever possible, the effectiveness of pain management methods on reducing neonates' pain-related reactivity (earliest reactions after the painful stimulus) versus regulation (later reactions that occur after the initial painful response) will be specified [38]. Although interrelated, the distinction of these two phases is warranted, as research has suggested that non-pharmacological pain management interventions may be more related to infants' pain levels in the regulatory phase, rather than the reactivity phase [17]. Finally, readers are drawn to a recent Cochrane Review that directly reviews the literature on 22 different non-pharmacological strategies for infant and young child procedural pain [38].

4.1. Proximal pain management methods

Proximal methods of pain management support newborns to achieve baseline states post-painful procedure and alleviate pain by providing soothing tactile stimuli before, during, and/or after the painful procedure. According to the Gate Control Theory [39], it may be that the signals elicited by the soothing stimuli travel up ascending pathways, inhibiting the nociceptive signals created by the noxious event, through endogenous mechanisms located along the spino-thalamic tract [40].

Pain management techniques that can be encompassed in this category include skin-to-skin contact (also known as kangaroo care), facilitated tucking (containing an infant by hand-hugging), swaddling (containing an infant with a blanket), sucking-related strategies (e.g., non-nutritive sucking on a pacifier or finger), rocking, and breast-feeding. Non-nutritive sucking, swaddling/tucking, and rocking/holding were determined to be promising pain management interventions for full-term neonates [38]. However, age differences emerged, with non-nutritive sucking failing to relieve preterm neonates' pain reactivity. Swaddling/tucking interventions and touch/massage showed promise for preterm infants [38]. Hartley, Miller, and Gephardt [41] conducted an additional review that supported these results, demonstrating the effectiveness of facilitated tucking at reducing pain in preterm newborns. The results of a randomized controlled trial on the effects of swaddling on acute pain in preterm neonates also revealed analgesic effects, with the swaddled group exhibiting lower pain scores and faster returns to baseline following a blood sampling procedure [42].

Furthermore, Pillai Riddell et al. [38] also concluded that sucking-related interventions and facilitated tucking/swaddling were shown to be effective at alleviating pain in the reactivity stage, while sucking-related interventions and rocking/holding demonstrated effectiveness during the regulation stage. The above findings are bolstered by a second review examining the combined effects of non-nutritive sucking on pain responses in neonates and older infants up to 4 months old. In this review, Taddio and colleagues [43] showed non-nutritive sucking to be effective in reducing infant pain-related distress.

Skin-to-skin care and co-bedding. Johnston et al. [44] concluded that skin-to-skin care is more beneficial at relieving both behavioural and physiological indicators of pain than standard care. Although the pain reduction effects of skin-to-skin care have been demonstrated, nurses have stated multiple challenges precluding them from providing this care to neonates in NICUs, such as heavy workload. Mothers' presence during acute procedures in order to provide skin-to-skin contact for their children was provided as a potential solution to this issue [32]. Another pain-management intervention related to proximity is co-bedding, the action of placing multiple newborns in a singular incubator. Co-bedding has been linked to a better regulated stress response following an acute procedure in neonates, as indicated by reduced cortisol levels and faster returns to baseline physiology [45].

Breastfeeding. Shah, Herbozo, Aliwalas, and Shah [46] led a

systematic review on the effects of breastfeeding on crying time and pain scores in full-term newborns and results revealed its effectiveness over other positioning interventions (e.g. swaddling; placing the neonate in a crib), placebos, and standard care. These findings were bolstered by another systematic review conducted in 2015 on the benefits of breastfeeding for analgesic purposes [47]. Fallah, Naserzadeh, Ferdosian, and Binesh [48] demonstrated more effective analgesia in breastfeeding compared to kangaroo care and swaddling in term neonates. Interestingly, providing newborn babies with breast milk via a syringe did not lead to the same analgesic effects as breastfeeding, potentially due to the latter reducing pain-related distress via multiple mechanisms due to the combination of holding- and sucking-related interventions with ingestion of a sweet-tasting substance [34]. This further points to the importance of including mothers in pain management implementations.

4.2. Distal pain management methods

Distal pain management interventions involve modifying the neonates' environment to achieve a diminished pain response and pain-related distress. This category includes strategies such as controlling the noise, lighting, and smells in the NICU.

Odours. Pillai Riddell et al. [38] found that environmental modifications, such as introducing familiar odours, were effective in relieving newborns' pain in the regulation phase.

Light. Light intensity has been shown to have negative effects on neonates in NICUs, while intermittent lighting has been associated with reductions in heart rate, strengthened biological rhythm, and better sleep quality and nutrition [49]. This concept has also been applied to research examining the potential analgesic effects of low lighting. For instance, a study exploring the effects of covering newborns' eyes during a painful procedure revealed a significant reduction in infants' behavioural pain responses solely when the pain intervention was executed after the procedure, not during [50]. However, reductions in the physiological domains of pain, such as heart rate and SaO₂ levels, were not observed; therefore, further studies examining the analgesic effects of light in NICUs are warranted.

Sound/music therapy. Previous studies have attempted to analyze the analgesic effects of sounds/music therapy in NICUs, posited to reduce pain by decreasing infants' state of arousal and pain-related behavioural responses [51]. However, studies have yielded mixed results. One type of sound therapy that has demonstrated analgesic qualities in both preterm and full-term neonates has been exposure to the mother's voice [52,53]. Additionally, listening to classical music was shown to be effective in reducing pain responses during routine heel lances [54]. Alternatively, Badr et al. [55] discovered that exposing neonates to lullabies or to music their mothers listened to during pregnancy had a positive impact on children's behavioural measures of pain, but not physiological. Other interventions, such as exposure to intrauterine sounds such as heart rate in an attempt to reduce pain reactivity have also shown promise [56].

4.3. Procedural pain management methods

It is important to remind readers that avoiding unnecessary painful procedures should always be the first line of pain management. However, when medically necessary, pain management implementations can also aim to achieve pain reduction by targeting and refining the medical procedure itself. Examples of procedural pain management techniques incorporated in this classification are choosing appropriate injection sites, sequencing vaccines suitably in an attempt to reduce their additive pain in order of least painful to most painful, and using aspiration versus no aspirations during vaccines. For instance, heel lances are the most commonly used procedures in NICUs for blood sampling [57]. However, a systematic review on heel lance versus venepuncture for neonate blood sampling concluded that venepuncture

yield lower pain scores on numerous validated measures of pain in full-term neonates [58]. Moreover, research analyzing the analgesic effects of adding upper limb massage to the vaccination procedure, i.e. prior to administering venepuncture, in a sample of preterm and full-term neonates has revealed lower pain scores in those who received the massage intervention [59].

A review that combined results from newborns with infants up to 6 months old determined that, when administering multiple vaccines, injecting the most painful one last produces lower overall distress in all ages [43].

4.4. Additive effects of combined pain management methods

As the research on infant pain matures, the use of a no pain management control group has evolved to become unacceptable. Some studies have thus analysed the additive analgesic effects of multiple combined pain management techniques to find more optimal ways of pain management, which will be reviewed next.

Research examining the combined effects of non-nutritive sucking and sucrose indicated an additive analgesic effect of non-nutritive sucking compared to sucrose alone. Furthermore, tucking/swaddling combined with non-nutritive sucking was superior compared to non-nutritive sucking alone [38]. Combined holding-related implementations (consisting of either cuddling and back-patting or swaddling, side-lying, swinging, sucking, and shushing) administered after the painful procedure have also been shown to reduce distress in newborns and infants up to 4 months old [43]. Finally, newborns displayed fewer pain-related behaviours (i.e., grimacing, squirming, limb and trunk extensions) when exposed to a combination of non-nutritive sucking, facilitated tucking, and sucrose than either of these interventions alone [60].

Compared to the combined effects of facilitated tucking, non-nutritive sucking, and oral glucose, the addition of music therapy has been linked to neonates displaying more stable physiological and behavioural responses, allowing nurses to complete the required routine procedures more efficiently [61]. Further support for the benefits of music on pain-related distress emerged from Qiu et al. [62], who examined the analgesic effects of Combined Music and Touch (CMT) intervention and concluded its effectiveness at reducing neonates' pain response as measured by the PIPP. Furthermore, Shah, Kadage, and Sinn [63] determined that, although the analgesic benefits of music therapy were comparable to those of sucrose in full term neonates, the combination of the two yielded the greatest level of pain relief.

Shah et al. [47] revealed an additive effect of breastfeeding when combined with a pharmacological pain management implementation, such as a topical anaesthetic. In NICUs where expressed breast milk was considered standard care, combining this procedure with skin-to-skin mother care was shown to be more beneficial at reducing neonates' pain [64].

Overall, it appears that combining certain pain management techniques may have stronger analgesic effects compared to administering individual techniques.

5. Future directions

Further research is warranted to bolster the support for the current review, particularly randomized controlled trials on adequately-powered samples that use methodological standards for interventional research. More fundamentally, current pain assessment (the bedrock of optimal pain management) is currently predicated on high levels of convergence of biological and behavioural measures of pain. However, there have been important challenges to the supposition. For instance, Slater et al. [65] revealed that, although oral sucrose was effective at reducing newborns' behavioural expressions of pain, it had no analgesic effect on the underlying nociceptive brain activity or spinal cord circuits. Jones et al. [66] have found that in high stress contexts, biological

and behavioural relationships are not seen (in contrary to strong relationships when infants show evidence of lower stress situations). Two other papers [50,55] suggested analgesic effects solely on pain-related behavioural expressions and not on the underlying physiology. Finally, it is important to recognize that there is large variability in infant pain responding. Basing the efficacy or effectiveness of any infant pain intervention by simplistically comparing group means without any disaggregation of this variability will not result in understanding the true treatment effects of an intervention [67].

6. Concluding notes

Given the large number of pain management techniques and the exponentially large number of potential combinations, it is impossible for any review to touch upon all these combinations. Thus, clinicians are likely best served by keeping in mind key principles of neonatal pain management as reviewed such as avoiding procedures, providing soothing tactile stimulation, helping an infant to feel contained, encouraging proximity to a caregiver before, during, and after a procedure and using pharmacological interventions that may be more apt to block or moderate nociception. Moreover, scientists are encouraged to look at challenges to current study methodologies to provide better data regarding the efficacy of different pain management techniques for infants.

Practice Points

- Hospitalized preterm neonates are frequently exposed to painful medical procedures
- Early neonatal pain exposure is linked to detrimental long-term outcomes
- Pain management methods are crucial in neonatal care
- Non-pharmacological pain management (proximal, distal, and procedural) methods have shown effectiveness at reducing neonates' pain responses
- Combining certain pain management techniques may have stronger analgesic effects compared to administering individual techniques

Research Directions

- Randomized controlled trials on adequately-powered samples analyzing the efficiency and effectiveness of pain management methods are needed
- Differentially examining the analgesic effects of pain management methods on infants' behavioural versus physiological pain responses must be conducted
- Acknowledging the large variability in infant pain responding in order to uncover the true treatment effects of interventions

Conflict of interest

The authors have no conflicts of interest to disclose.

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